A six-membered cyclic phosphate of foremost biological importance is cyclic AMP. The ring of cyclic AMP is actually a derivative of 1,3 cGP backbone. Other cyclic phosphates which were detected in biological systems include glucose cyclic phosphodiester (Leloir, 1951), 2',3'-cyclic phosphodiester (Markham and Smith, 1952), riboflavin-4',5'-cyclic phosphodiester (Forrest and Todd, 1950), myoinositol-1,2-cyclic phosphodiester (Dawson *et al.,* 1971) and cyclic lysophosphatidic acid (Friedman *et al.,* 1996).

Except for cyclic AMP and cyclic GMP, which have been extensively studied, no specific biological activities have been so far assigned to the other biological cyclic phosphates.

There are several kinds of disorders and diseases, which result from deterioration of areas of the brain and loss of neurons. One example of such diseases are neurodegenerative diseases such as Parkinson's disease (PD). Such diseases often involve degeneration of dopamine-producing neurons. Current therapeutic methods are mostly aimed at continuous stimulation of dopamine receptors by drugs, which, although initially providing symptomatic relief, gradually lose effectiveness. Furthermore, such drugs do not prevent the progressive degeneration of dopaminergic neurons characteristics of such diseases.

A large number of growth factors such as nerve growth factor (NGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), insulin-like growth factor, brain derived growth factor and glial derived neurotrophic factor (Knusel B., *et al.*, 1990; Knusel *et al.*, 1991; Linn *et al.*, 1993) stimulate dopaminergic neuron survival and differentiation *in vitro.* In animal models involving induction of Parkinson's disease, the induced animals show improved behavior and an increase in tyrosine hydroxylase (TH), the key enzyme in the dopamine production pathway immunoreactvity when treated with factors like GDNF (Tomac, A. *et al.* 1995) and ciliary neurotrophic factor (CNTF) (Hagg, T. and Varon 1993).

ameliorating or preventing the enhancement of the treated condition and related symptoms.

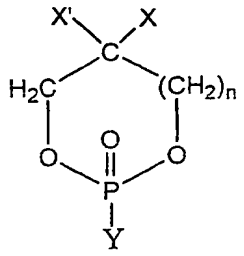
Neural promoting activity – this term encompasses a variety of neural related activities which may be promoted in target cells upon their contact with the *CPP* used in the invention. Such activities include but are not limited to promotion of nerve growth, provision of dopaminotrophic supporting environment in a diseased brain, prevention of nerve degeneration, and nerve rescue.

Prevention or treatment – the term prevention of disorders or diseases is to be understood in accordance with the invention as a reduction in the probability of the appearance of such disorders or diseases in an individual having a high predisposition of developing such disorders or diseases, reducing the extent of the symptoms associated with such disorders and diseases when they occur or completely preventing their appearance.

SUMMARY OF THE INVENTION

In accordance with the invention new derivatives of 1,3-cyclic propandiol phosphate are provided that are capable of stimulating cells.

The present invention thus provides, by a first of its aspects, a compound of formula I



or pharmaceutically acceptable salts thereof,

wherein

n is 0 or 1;

X is hydrogen, O-R, NH-R, NO_2, or N-(C=O)-R;

X' is hydrogen or CH_2OH;

Y is O-R_1, NH-R_1;

R is hydrogen, linear or branched alkyl, linear or branched acyl, substituted or non-substituted aryl or araalkyl residue;

R_1 is hydrogen, linear or branched alkyl, linear or branched acyl, substituted or non-substiuted aryl, alkylcarboxy ester or alkyl-N-R_2R_3;

R_2 and R_3 are independently hydrogen or an alkyl group;

provided that when X and X' are hydrogen and n=0, Y is not O-R_1 wherein R_1 is hydrogen, alkyl or aryl; and provided that when X' is CH_2OH then X is NH-R or NO_2.

As used herein the term *"alkyl"* refers to an alkyl group having from 1 to 24 carbon atoms, e.g. preferably from 3 carbon atoms to 20 carbon atoms, most preferably from 5 carbon atoms to 15 carbon atoms; the term *"acyl"* refers to an aliphatic saturated or unsaturated C_1 - C_{24} acyl group, preferably an acyl group having an even number of carbon atoms, most preferably an acyl group derived from a natural fatty acid such as a saturated aliphatic acyl group selected from acetyl, butyryl, caproyl, octanoyl, decanoyl, lauroyl, myristyl, palmitoyl and stearoyl, or an unsaturated aliphatic acyl group selected from palmitoleyl, oleyl, linoleyl, and ricinoleyl; and the term *"aryl"* refers to a mono- or poly-carbocyclic aryl group, most preferably phenyl, optionally substituted by C_1 - C_4 alkyl, halogen and/or hydroxy.

In one embodiment, Y is a hydroxyl group and X is O-oleoyl, O-benzyl, O-$CH_2COOCH_2CH_3$, NH-benzyl or NH-caproyl.

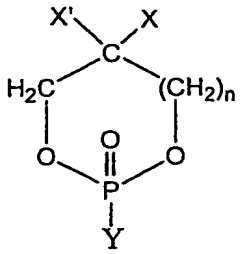
In another embodiment X is hydrogen and Y is O-acetyl or NH-CH_3.

The present invention further provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as an active ingredient, a compound of the general formula I. A preferred use of said composition is for stimulation of target cells.

The *CPP* used in the invention may exert one of many neural promoting activities including but not limited to promotion of neuronal outgrowth, promotion

CLAIMS:

1. A compound of the following formula (I):



or pharmaceutically acceptable salts thereof,

wherein:

n is 0 or 1;

X is hydrogen, O-R, NH-R, NO_2, or N-(C=O)-R;

X' is hydrogen or CH_2OH;

Y is O-R_1, NH-R_1;

R is hydrogen, linear or branched alkyl, linear or branched acyl, substituted or non-substituted aryl or araalkyl residue;

R_1 is hydrogen, linear or branched alkyl, linear or branched acyl, substituted or non-substiuted aryl, alkylcarboxy ester or alkyl-N-R_2R_3;

R_2 and R_3 are independently hydrogen or an alkyl group;

alkyl is an alkyl group having from 1 to 24 carbon atoms, preferably from 3 carbon atoms to 20 carbon atoms, most preferably from 5 carbon atoms to 15 carbon atoms;

wherein acyl is an aliphatic saturated or unsaturated C_1 - C_{24} acyl group, preferably an acyl group having an even number of carbon atoms, and most preferably an acyl group derived from a natural fatty acid such as a saturated aliphatic acyl group or an unsaturated aliphatic acyl group;

aryl is a to a mono- or poly-carbocyclic aryl group, most preferably phenyl, optionally substituted by C_1-C_4 -alkyl, halogen and/or hydroxy;

provided that when X and X' are hydrogen and n=0, Y is not O-R_1 wherein R_1 is hydrogen, alkyl or aryl and further provided that when X' is CH_2OH then X is NH-R or NO_2.

2. A compound according to claim 1, wherein the acyl moiety is selected from the group comprising of acetyl, butyryl, caproyl, octanoyl, decanoyl, lauroyl, myristyl, palmitoyl and stearoyl, palmitoleyl, oleyl, linoleyl, and ricinoleyl.

3. A compound according to claim 1 wherein Y is OH and X is O-R or NH-R; wherein R is a linear or branched alkyl or linear or branched acyl.

4. A compound according to claim 1 wherein X is hydrogen and Y is O-R_1 or NH-R_1; wherein R_1 is a linear or branched acyl.

5. Compounds of formula I according to claim 1 selected from the group consisting of:

(a) 1,3-cyclic propandiol phosphate-5-oleoyl;

(b) 1,3-cyclic propandiol phosphate-5- benzyloxy;

(c) 1,3-cyclic propandiol phosphate-5- benzylamino;

(d) 1,3-cyclic propandiol phosphate-5- caproylamido;

(e) 1,3-cyclic propandiol phosphate-2-benzyloxy;

(f) 1,3-cyclic propandiol phosphate-2- acetyloxy;

(g) 1,3-cyclic propandiol phosphate-2-methylamino;

(h) 1,3-cyclic propandiol phosphate-5-glycine ethylester;

(i) 2-methyl 1,3-cyclic propanediol phosphate;

(j) 1-methyl 1,3-cyclic propanediol phosphate;

(k) 2-dimethylamine ethyl ester 1,3-cyclic propanediol phosphate;

(l) 1,3-cyclic propanediol phosphoamidate;

(m) 1,3-cyclic propanediol N-ethyl phosphoamidate;

(n) 1,3-cyclic propanediol phosphoamidate glycine ethylester;

(o) 2-benzyloxy 1,3-chloropropanediol phosphate;

(p) 2-caproimido 1,3-chloropropanediol phosphate;

(q) 5-amino-5-hydroxymethyl-2-oxo-2λ5-[1,3,2]dioxaphosphinan-2-ol;

(r) 5-nitro-5-hydroxymethyl-2-oxo-2λ5-[1,3,2]dioxaphosphinan-2-ol;

or pharmaceutically acceptable salts thereof.

6. A pharmaceutical composition comprising a pharmaceutical acceptable carrier and, as an active ingredient, a compound of the general formula (I) in claim 1 or pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition according to claim 6, for promoting neural activity.

8. A pharmaceutical composition according to claim 7, wherein said neural activity is selected from the group consisting of promotion of neuronal outgrowth, promotion of nerve growth, provision of dopaminotrophic supporting environment in a diseased portion of the brain, prevention of nerve degeneration and nerve rescue.

9. A pharmaceutical composition according to claim 8, wherein said neuronal outgrowth is axonal growth or axonal branching.

10. A pharmaceutical composition according to claim 6, for the prevention or treatment of disorders and diseases which can be prevented or treated by activating neural cells.

11. A pharmaceutical composition according to claim 8, wherein said disorder and disease are schizophrenia, dementia or disorder resulting from learning disabilities.

12. A pharmaceutical composition according to any one of claims 6 to 11 wherein the compound of formula I is selected from the group consisting of

(a) 1,3-cyclic propandiol phosphate-5-oleoyl;

(b) 1,3-cyclic propandiol phosphate-5- benzyloxy;

(c) 1,3-cyclic propandiol phosphate-5- benzylamino;

(d) 1,3-cyclic propandiol phosphate-5- caproylamido;

(e) 1,3-cyclic propandiol phosphate-2-benzyloxy;

(f) 1,3-cyclic propandiol phosphate-2- acetyloxy;

(g) 1,3-cyclic propandiol phosphate-2-methylamino;

(h) 1,3-cyclic propandiol phosphate-5-glycine ethylester;

(i) 2-methyl 1,3-cyclic propanediol phosphate;

(j) 1-methyl 1,3-cyclic propanediol phosphate;

(k) 2-dimethylamine ethyl ester 1,3-cyclic propanediol phosphate;

(l) 1,3-cyclic propanediol phosphoamidate;

(m) 1,3-cyclic propanediol N-ethyl phosphoamidate;

(n) 1,3-cyclic propanediol phosphoamidate glycine ethylester;

(o) 2-benzyloxy 1,3-chloropropanediol phosphate;

(p) 2-caproimido 1,3-chloropropanediol phosphate;

(q) 5-amino-5-hydroxymethyl-2-oxo-2λ5-[1,3,2]dioxaphosphinan-2-ol;

(r) 5-nitro-5-hydroxymethyl-2-oxo-2λ5-[1,3,2]dioxaphosphinan-2-ol;

or pharmaceutically acceptable salts thereof.

13. Use of a compound of formula I for the preparation of a medicament for treating disorders and diseases which can be prevented or treated by activating neural cells, substantially as described in the specification.

14. Use according to claim 13, wherein said neural activity is selected from the group consisting of promotion of neuronal outgrowth, promotion of nerve growth, provision of dopaminotrophic supporting environment in a diseased portion of the brain, prevention of nerve degeneration and nerve rescue.